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13. ABSTRACT *(Maximum 200 words)*

The experiments conducted during the three years of this contract and the continued work (until the end of 1990) were very productive. We have made considerable progress toward achieving the goal of developing a pharmacological treatment regimen for promoting functional recovery after traumatic brain injury (TBI). This report summarizes the objectives, results and discusses the significance of published findings as well as several completed but not yet published experiments. These research findings are currently being replicated and/or written for publication.

The research supported by this contract utilized a multi-disciplinary approach to analyze some effects of pharmacological intervention on functional recovery from locomotor deficits after a unilateral injury to the right sensorimotor cortex (SMCX) in the rat: First, the well documented beneficial effect of a single dose of d-amphetamine (AMPH) on functional recovery after SMCX ablation was extended to different severities of SMCX contusion. Second, the effects of systemic administration of drugs affecting catecholaminergic

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neurotransmission and the effects of direct intracerebroventricular infusion of catecholamine (CA) neurotransmitters were examined in the SMCX contusion model. Third, we investigated putative mechanisms by which AMPH facilitates recovery from hemiplegia, as measured by our beam walking (BW) task after cortical contusion. Physiological and/or phamacological manipulations which alleviate locomotor deficits after SMCX contusion were evaluated for their effects upon CA metabolism, cerebral glucose utilization, and oxidative metabolism. Lastly, anatomical descriptions of primary and secondary neuronal death following SMCX contusion injury is in progress. At this time, we have examined the effects of anesthetic conditions, and pharmacological treatment with AMPH, methoxamine, or ketamine on neuropathological sequalae after TBI.

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FOREWORD

In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

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INTRODUCTION

There is a clear need for a better understanding of the pathophysiology after brain injury in order to develop medical treatments to promote functional recovery. Currently, there is no accepted medical treatment that alleviates or even significantly diminishes morbidity and mortality after brain injury. Traditionally, attempts have been made to limit the spread of cerebral damage by improving cerebral blood flow, reducing metabolic demands in ischemic tissue, and relieving concomitant effects, such as hemorrhage, edema, or elevated intracranial pressure. These therapies have not resulted in convincing improvement of functional recovery (1).

Traumatic brain injury (TBI) results in permanent, significant impairment of the physical, psychosocial and/or cognitive functional abilities of 30,000 to 50,000 individuals in the United States each year. Severe TBI occurs more frequently in combat soldiers than in the general public, where closed head injury and concussion are more prevalent. In military and civilian situations, brain-injured patients require prolonged, costly, and labor intensive care. In fact, within the civilian population, the average per case treatment cost for the first year following severe TBI, excluding rehabilitation, was $105,350, in 1982-83 (2). Accelerated recovery from mild brain injury could hasten the return of individuals to their military or civilian duties. Whereas, in the case of severe injuries pharmacological intervention could significantly reduce hospitilization time and costs. A better understanding of the mechanisms governing spontaneous recovery following brain injury may provide insight for the development of treatment methods which can accelerate functional recovery and/or increase the level of recovery obtained.

The three years of research supported by this contract examined a promising new approach for ameliorating behavioral deficits following TBI. These studies investigated the effects of pharmacological manipulation of catecholamine neurotransmitters (CAs) upon behavioral, biochemical, metabolic, and anatomical measures in a rat model of TBI. The first year of research examined; 1) the effect of delayed administration of d-amphetamine (AMPH), 2) selective CA receptor agonists and antagonists, and 3) electroconvulsive seizures on functional recovery from hemiplegia. In addition, the extent of cortical necrotic cavitation was examined following focal impact injuries after delayed administration of AMPH or saline. The results indicated a role for NE in behavioral recovery and its maintenance after cortical contusion and suggested the importance of alpha noradrenergic receptors in mediating these effects. However, AMPH enhanced recovery is unlikely due to spared cortical tissue, since no effect of AMPH upon cortical necrosis was observed regardless of injury severity (for a detailed description of methods and results see ref. 3).

During the second year of this contract, we examined: 1) the effect of intracerebroventricular (ICV) infusion of either NE or DA 24 hours following contusion injury on functional recovery, 2) the effect of partial locus coeruleus (LC) lesion prior to contusion on behavior and brain NE levels, 3) the effect of a systemic injection of morphine 24 hours post-contusion injury on functional recovery, and 4) the effect of contusion and AMPH treatment on cerebral glucose metabolism. The results of these studies further supported the hypothesis that at least one aspect of AMPH facilitated locomotor recovery

is via the noradrenergic system (for a detailed description of methods and results see ref. 4).

In the third year, we began analysis of neurochemical changes and measurements of oxidative metabolism as well as assessment of histopathological sequalae following SMCX injury. First; we described the effects of contusion, ablation, anesthesia, AMPH, and the alpha-1 agonist methoxamine upon secondary cell death. Second; we assessed changes of monoamines and their metabolite levels after SMCX ablation, which does not produce remote secondary cell death as does TBI. Third; we studied the effect of AMPH upon monoamines and their metabolite levels after SMCX ablation. Fourth; we reported that reserpine pretreatment blocks AMPH facilitation of BW recovery, providing additional support for our hypothesis that NE and not DA is involved in the AMPH effect on recovery of function (for a detailed description of methods and results see ref. 5).

The results of these studies suggest that monoamine metabolism within structures remote from cortical injury, play a key role in behavioral deficits, metabolic abnormalities, and secondary cell death. These results, taken together, lend support for the theory of diaschisis. The 1988 edition of Dorland's Medical Dictionary defines diaschisis as follows. ".. the loss of function and electrical activity caused by cerebral lesions in areas which are remote from the lesion but which are neuronally connected to it.." (6). Based on this work, we proposed a revision of Von Monakow's controversial and often misunderstood theory of diaschisis (7) to explain spontaneous recovery and a mechanism of pharmacological treatment(s) enhancing recovery of function. Given our results and their implications, we have made considerable progress toward achieving the goal of developing a pharmacological treatment regimen for promoting functional recovery after TBI.

SUMMARY

A single dose of AMPH, when combined with symptom relevant experience (SRE), administered 24 hours postcontusion (400 g/cm^2) injury, will facilitate the rate of locomotor recovery as measured on a beam walking (BW) task. The aim of this research was to elucidate the mechanism(s) by which AMPH administration facilitates recovery of locomotor function (7, 8, 9, 10, 11, 12, 13, 14, 15, 16). Significant progress has been made in understanding the behavioral, biochemical, metabolic, and anatomical consequences of this rat model of TBI.

Pharmacological studies indicate that promotion of noradrenergic neurotransmission combined with SRE will enhance performance on some but not all sensory-motor tasks. Following 400 gm/cm^2 SMCX contusion injury, the accuracy of ballistic limb movements such as those used in locomotion are improved following the administration of AMPH, while fine motor coordination, such as forepaw grasping ability, is not detectably affected by AMPH treatment. In addition, the effect of AMPH on locomotor performance is also limited by the severity of injury. Following mild cortical injuries (200gm/cm^2 SMCX contusion), spontaneous recovery occurs so quickly on the BW task that an AMPH effect is not detectable. Recovery from BW deficits after more severe traumatic brain injuries (600 or 1000gm/cm^2) are not facilitated by AMPH administration. Such severe injuries may require a different treatment approach or may simply be intractable (3, 9).

It is difficult to determine the mechanism(s) of AMPH-facilitated recovery due to the diverse effects of AMPH within the CNS. In the normal rat, AMPH dramatically increases the release of NE (17, 18, 19). However, AMPH also strongly influences dopamine (DA) (17, 20), gamma-aminobutyric acid (21), acetylcholine (22), and serotonin (23, 24, 25) neurotransmission. The CAs have been implicated in mediating the AMPH/SRE enhancement of recovery following TBI because the broad-spectrum CA receptor antagonist, haloperidol, blocks AMPH facilitation of BW performance (8). More specifically, the NE alpha$_1$ antagonist, phenoxybenzamine, also blocks AMPH/SRE facilitation of locomotor performance indicating that not just the NE system but probably the alpha$_1$ NE receptors are inportant in the AMPH/SRE effect (26).

In an effort to further clarify the role of the CA neurotransmitters in AMPH-facilitated recovery of locomotor function, specific pre- and postsynaptic agonists and antagonists of both NE and DA receptors were examined following SMCX injury (See appendix 1-A and 1-B). Neither the DA agonist apomorphine nor the beta-adrenergic antagonist, propranalol, were found to be effective in altering recovery of function following lesions of the SMCX. Methoxamine and phenylephrine, agonists of the alpha$_1$-adrenergic receptor, had slight, but not statistically significant, facilitory effects on recovery of BW ability following SMCX contusion (3). Recent observations and further analysis of previously collected data indicate that methoxamine may have a disability specific facilitory effect on recovery of function. The effects of alpha$_1$ agonists are currently being re-evaluated in the SMCX contusion model.

Whereas, the effect of alpha$_1$ agonists upon locomotor recovery are currently unclear, the effect of alpha$_1$-adrenergic antagonists are markedly detrimental for recovery of function. The alpha$_1$-adrenergic antagonist,

prazosin, will retard locomotor recovery following SMCX contusion, but not ablation. The cause of this differential effect of prazosin administration after SMCX injury is unknown, although there are striking differences of biochemical, metabolic, and morphologic sequelae following SMCX contusion and ablation injuries (described below).

The alpha$_2$-noradrenergic receptor, classically thought of as a presynaptic autoreceptor (except in the locus coeruleus [LC] where alpha$_2$ receptors are on the neuronal somata), also influence behavioral recovery after TBI. Specifically, the alpha$_2$ antagonist, yohimbine facilitates behavioral recovery after SMCX ablation but only approaches significance in the contusion model. Furthermore, the alpha$_2$ agonist, clonidine, slows functional recovery only after SMCX contusion (please note that alpha$_2$ NE receptor agonists will decrease NE release, whereas, alpha$_2$ antagonists will stimulate NE release).

In addition to detrimental effects on recovery of function, the alpha$_1$ antagonists have dramatic effects on the maintenance of BW ability in animals recovered from TBI. The alpha$_1$-adrenergic antagonists, prazosin and phenoxybenzamine, reinstate BW deficits in contused or ablated animals following complete recovery of beam walking ability. The reinstatement is unlikely to be due to a nonspecific drug effect since the deficits reappear only in the limbs contralateral to the cortical injury (11). Similarly, the alpha$_2$ agonist clonidine reinstates BW deficits following recovery from contusion or ablation (See appendix 1-C).

One possible mechanism of AMPH/SRE facilitated recovery is to reduce the extent of cortical cavitation after SMCX contusion. Description of cortical cavitation following TBI has revealed a number of interesting observations. First, the average volume of cavitation in animals receiving 800 g/cm^2 impact injury was significantly larger than those receiving 400 g/cm^2 impact injury. Accordingly, more severe deficits and slower spontaneous recovery were present after an 800 g/cm^2 as compared to a 400 g/cm^2 contusion impact. Interestingly, a single dose of AMPH given 24 hours after 400 g/cm^2 contusion injury accelerates BW recovery compared to saline controls, however, regardless of the severity of contusion (200-1000 g/cm^2 focal impact injury), the average volume of cavitation for animals receiving AMPH was not different from saline controls.

The effects of electroconvulsive shocks (ECS), were examined on recovery of function and cortical cavitation necrosis since seizures frequently develop following TBI (27). Additionally, seizures enhance NE turnover (28, 29). Rats receiving a 600 g/cm^2 contusion followed by 2 ECS performed significantly better on the BW task than the animals receiving only a contusion. Animals receiving 7 ECSs after contusion were not significantly different from the contusion alone control group on the BW task. In contrast to the effect of ECS upon BW ability, animals receiving 7 ECS had significantly smaller areas of cortical necrosis than animals receiving contusion alone while the reduction in area of necrosis was not significant for animals given 2 ECS.

During the second year, several additional lines of evidence supported a key role for NE in AMPH facilitated locomotor recovery. Intracerebroventricular infusion of NE, but not DA, facilitated motor recovery in a manner similar to AMPH. Additionally, Boyeson et al. reported that localized infusion of NE into the contralateral. but not the ipsilateral.

cerebellar cortex facilitates recovery from hemiplegia (30).

The LC is the major source of NE-containing neurons in the brain with efferents projecting to the cerebral cortex and cerebellum, among other areas (31, 32). Since the majority of pharmacological data supports a role of the noradrenergic system, we proposed that AMPH and other drugs facilitating BW recovery after SMCX injury, act via the LC or its axonal terminals, promoting release of NE throughout the brain. Amphetamine inhibits LC neuronal firing, through activation of the alpha$_2$ autoreceptor (32, 33). However, AMPH also induces massive release of NE and blocks reuptake (17). The net effect of AMPH is to produce sustained NE synaptic activation independent of axonal impulse flow. In fact, L'Heureux, et al. (34) report a 450% AMPH induced increase of cortical NE release above basal levels. To test the hypothesis that AMPH facilitates recovery through a massive release of NE during SRE, the LC was bilaterally lesioned prior to SMCX contusion. Amphetamine still facilitated recovery following SMCX contusion in animals with LC lesions that reduced cortical NE by 50%. Two explanations accounting for this unexpected observation are plausible due to partial LC lesions; 1) sprouting of remaining noradrenergic terminals and 2) receptor supersensitivity of the denervated postsynaptic cells.

Similar to the effects of noradrenergic agonists, a single dose of morphine in combination with SRE, also facilitated locomotor recovery. The effect of morphine occurs in a narrow dose range and is dependent degree upon initial BW deficit. Only animals receiving 10mg/kg and achieving a predrug score of 3 (See table 1, ref. 5) exhibited enhanced BW ability. More severely disabled animals, those receiving a predrug score of 2, did not show facilitated BW recovery after morphine administration. Higher and lower doses of morphine were ineffective in facilitating BW recovery. These observations were unexpected given previous lesion studies and the effects of morphine in these models (35, 36). The ability of morphine to promote locomotor recovery may be mediated through a noradrenergic mechanism since morphine is reported to increase LC activity (37 and 38 but see 39 and 40). Given this and the above mentioned findings, the bulk of the evidence suggests that NE acting at alpha receptors is critical for the facilitation and maintenance of functional recovery in this rat model of TBI.

Another possible mechanism of the AMPH/SRE facilitation of recovery from hemiplegia is the alleviation of metabolic disturbances resulting from TBI. The C^{14}-2-deoxy-d-glucose autoradiographic (2-DG) method (41) was used to measure local cerebral glucose utilization (LCGU) following AMPH or saline administration after TBI. In animals receiving saline, widespread bilateral depression of LCGU is observed two days following SMCX contusion injury in cortical and subcortical structures. Administration of AMPH 24 hours post-injury reversed the hypometabolic state within structures contralateral to the contusion injury. In addition, AMPH administration improved the observed hypometabolism in the ipsilateral caudate/putamen and cerebral cortex. Several extrapyramidal structures exhibit decreased LCGU following TBI of the SMCX. These areas include, the substantia nigra (SN) ipsilateral to the injury, compared to the contralateral SN. This effect of injury was alleviated in the AMPH-treated contused group compared to saline controls. This TBI induced hypometabolism recovered spontaneously in animals administered saline. Like

the reduced LCGU in the SN of saline control animals, hypometabolic conditions, in all other brain regions measured, are lessened at 6 days and absent 16 days after TBI.

Six days post-contusion an increased level of 2-DG uptake is observed in and confined to the ipsilateral hippocampal CA3 region. This hypermetabolism is normalized by treatment with AMPH 24 hours post-TBI. This hypermetabolic state was not observed 2 days postcontusion and dissipates by 16 days after injury.

In the third year of this contract we extended our investigation of the metabolic sequalae following TBI. Histochemical studies of oxidative metabolism using a stain for the mitochondrial enzyme cytochrome oxidase (CYO)(42) following SMCX ablation or contusion showed striking differences in the profiles of postlesion oxidative metabolism (43). Contusion of the SMCX produces a hypermetabolic state (as measured by increased CYO staining density) in the entorhinal, auditory, and pyriform cortices at 2 days postinjury which is not observed 2 days after SMCX ablation. A single dose of AMPH given 24 hours post-contusion will alleviate the hypermetabolism in the entorhinal and auditory cortices but not in the pyriform cortex (43). This oxidative hypermetabolism is less profound at 6 days postinjury and absent at 16 days postcontusion. The CA3 pyramidal cells receive both direct and indirect (via dentate granule cells) input from the entorhinal cortex. The entorhinal cortex and hippocampal regions (i.e. CA3) form a functional neural circuit which must be intact for the consolidation of memory (44). Given that AMPH alleviated hypermetabolism in this neural circuit (as measured by LCGU and CYO), it is interesting that AMPH is reported to alleviate memory deficits following cortical lesions (15), a common symptom of TBI in man.

The observed metabolic disturbances remote from the site of cortical damage, its spontaneous dissipation, and the normalizing effect of AMPH treatment provide support for the theory of diaschisis. Remote metabolic disturbances and subsequent normalization may contribute to observed behavioral deficits and their spontaneous recovery, respectively. The effect of AMPH and SRE may be to accelerate the resumption of normal metabolic and biochemical processes within neuronal circuits necessary for locomotor function. Additionally, the different metabolic sequelae produced following SMCX contusion and ablation may be related to posttraumatic secondary cell death observed after contusion but not ablation.

Paralleling metabolic disturbances, neuropathology remote from the site of cortical impact was studied during the period of this contract. Interesting results concerning primary and secondary neuronal death following TBI have been obtained from the reexamination of histology from previous experiments and recent studies. We define primary reactions as due to cellular degeneration caused by the rupture of the extracelluiar membrane or intracellular organelles as a direct result of the impact forces and "secondary" as cellular degeneration caused by the sequelae of the impact forces other than the rupture of membranes or organelles that is incompatable with the survival of the neuron; usually considered to be remote from the site of impact. The SMCX contusion and ablation models produce strikingly different patterns of neuropathology remote from very similar areas of cortical cavitation. The SMCX ablation model was used to examine antero- and retrograde degeneration due to

the removal of the SMCX, in the absence of the mechanical forces produced by the SMCX contusion model. Unilateral SMCX contusion produces gliosis and/or neuronal loss in the ipsilateral medial geniculate nucleus (MGN), CA3 region of the hippocampus (CA3), dorsolateral striatum (DLS), and thalamic ventral basal complex (TVBC) when performed under short duration halothane (less than 10 min.) or pentobarbitol anesthesia. The neuronal loss and gliosis in the TVBC is also observed following SMCX ablation. The neuropathology within the TVBC is likely due to retrograde degeneration of thalamocortical neurons initiated by axonal injury following contusion or ablation of the SMCX. In contrast, the neuronal loss in the DLS, CA3, and MGN is unlikely due to antero- or retrograde degeneration of neuronal pathways since gliosis and/or cell death within these nuclei are not observed after SMCX ablation.

Given that our model of SMCX contusion causes massive release of glutamate (45), some of these secondary effects may be the result from glutamate mediated excitotoxicity. Contusions conducted under a low dose of ketamine, a glutamate receptor antagonist, specific for the NMDA glutamate receptor subtype, combined with a low dose of pentobarbital significantly attenuate hippocampal CA3, DLS, and MGN cell loss. These effects may be due to the blockade of excitatory amino acid induced excitotocicity, but other factors such as altered cerebral blood flow or reduced body temperature may also be responsible for the effects produced by ketamine. Studies of cerebral blood flow following TBI have just begun. Additionally, postcontusion administration (5 min) of high dose ketamine afforded significant protection of hippocampal CA3 pyramidal neurons and significantly decreased the volume of cortical necrosis. The reduction of CA3 cell loss by postcontusion administration of high dose ketamine is not evident at two days postcontusion, but is quite dramatic at 20 days after injury. However, recent work has failed to replicate the neuroprotective effect of postcontusion ketamine administration. Investigations have been undertaken to study these discrepant observations.

To further refine our model of TBI, systematic evaluation of anesthetic effects upon secondary cell death and functional recovery were conducted. No effects of anesthetic condition on TVBC neuronal loss and gliosis were detected. However, thalamic gliosis was significantly correlated with the number of trials contused animals required to recover from hemiplegic conditions. Presumably, the TVBC pathology is due to the axotomy of thalamocortical neurons and the severity of the TVBC neuronal loss and gliosis is an index of the extent of SMCX injured. As with the TVBC pathology, no effects of anesthetic conditions on BW recovery rate were detected.

While AMPH administration had no detectable effects on secondary neuropathology, a single administration of the alpha$_1$ noradrenergic agonist, methoxamine (8 mg/kg, ip.) 24 hours following TBI to the rat SMCX significantly reduced hippocampal CA3 pyramidal cell loss (46). No effects of methoxamine (8 mg/kg, ip.) on gliosis and/or cell loss in the cortex, MGN, or DLS were observed. The basis of this neuroprotective effect of methoxamine in this study is unknown but similar effects of methoxamine have been reported in a gerbil stroke model (47). One possible reason for the lack of an AMPH effect and protection by methoxamine, is that AMPH is a very weak false transmitter at NE receptors. Additionally, AMPH evoked NE release within the hippocampus is persumably attenuated due to depletion of NE stores after TBI (48). Lastly,

released NE occupies both alpha and beta noradrenergic receptors which may cancel the neuroprotective effect mediated solely by alpha$_1$ agonists. Other possible mechanisms of the neuroprotective effect of methoxamine include: hypothermia and/or attenuation of excitotoxicity by inhibition of CA3 pyramidal cells or their afferent inputs.

A prominent sequela of our model of TBI is enlargement of the ipsilateral ventricle. This is consistently found after focal cortical contusion regardless of extent of cortical necrosis. The magnitude of ventricular ventricular enlargement after contusion is NOT correlated with the volume of necrotic cavitation. The magnitude of venrticular dilation after SMCX ablation is much less than that observed after contusion (49). Furthermore, the ependymal lining of the ventricles appears disrupted following contusion, but not ablation. Preliminary observations indicate gliosis adjacent to the ependymal breakdown in the enlarged ventricles after TBI. The gliotic reaction near the ventricle is not observed after ablation injury, as it is after contusion injury. Since, posttraumatic hydrocephalus is an often reported consequence of brain injury in humans, our model of TBI could prove useful in delineating the mechanisms of this reaction.

Studies of some neurochemical changes following SMCX lesions were done using high performance liquid chromatography. The purpose of these studies were to assess changes of the levels of stored monoamines and their metabolites after right SMCX injury. We also investigated the effect of AMPH administration on monoamine and metabolite levels after SMCX injury.

The data from these investigations indicate that at 2 days after unilateral SMCX ablation there is a bilateral depression of NE, DA, and the DA metabolite 3,4-dihydroxy-phenylacetic acid (DOPAC) levels. In contrast, the metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA) is significantly elevated ipsilateral to the injury. This diffuse monoamine respose to injury is likely a result of damage to the cortical terminals axons of the LC by the SMCX ablation. The resulting retrograde reaction in LC neurons and depression of activity may result from a change from transmitter synthesis to repair processes (50).

There is some support for the hypothesis that hemiplegia after SMCX injury is due, in part, to reduced NE in the cerebellum because of LC depression (7, 9, 11, 16). Infusion of NE into the contralateral, but not the ipsilateral, cerebellar cortex facilitates recovery from hemiplegia (30). However, no significant effect of SMCX injury or AMPH treatment upon NE or 3-methoxy-4-hydroxyphenylglycol (MHPG) levels (NE metabolite) were observed within the contralateral cerebellar cortex. The proposed microdialysis/HPLC experiments, a more sensitive and reliable measure of monoaminergic activity, may detect effects on NE release in the cerebellum.

The general finding of a widespread depression of monoamine levels 2 days after focal cortical injury, and the alleviation of this depressed activity by a single dose of AMPH, may be the basis for AMPH facilitation of behavioral and metabolic recovery after cortical injury.

Analysis of NE, MHPG, DA, and DOPAC levels 16 days after right SMCX contusion revealed no significant effect of either SMCX ablation or AMPH treatment (3). It is likely, the monoamine changes observed at two days post-injury spontaneously recovery to levels of non-injured controls by day

16. Monoamine levels 16 days after SMCX ablation are currently being assessed.

In addition, reserpine pretreatment blocks the AMPH/SRE-facilitation of locomotor recovery. In rats administered AMPH, reserpine pretreatment will selectively diminish the release of NE to negligible levels without significant effects on the release of DA (20). These data taken together indicate that the AMPH/SRE effect is most likely due to enhanced NE release.

In summary, these data strongly support the proposed central role of the noradrenergic system in mediation of AMPH/SRE facilitation of locomotor recovery. Although certainly not a panacea, the beneficial effects observed upon behavioral deficits, neurochemical and metabolic abnormalities, and secondary cell death through administration of pharmacological agents which promote noradrenergic function are certainly promising, warranting continued research and preclinical trials.

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APPENDIX 1-A

SENSORIMOTOR CORTEX ABLATION MODEL

DRUGS TESTED FOR EFFECTS ON RECOVERY RATE

Catecholamine Agonists

d-Amphetamine
monoamine agonist[1]
0.5 or 1 mg/kg,
No Significant (N.S.) effects
2 and 4 mg/kg,
significant facilitation[2,3]

Methylphenidate
Catecholamine agonist[5]
3.0 to 30 mg/kg, N.S. effects except
10 mg/kg significant facilitation[6]

Phenylpropanolamine
Catecholamine agonist[5]
10 mg/kg, N.S. effects
15 and 20 mg/kg significant
facilitation[3]

Phentermine
Catecholamine agonist[5]
6 or 24 mg/kg N.S. effects
12 mg/kg significant facilitation[3]

Catecholamine Antagonists

Haloperidol
Catecholamine antagonist[5]
.4 mg/kg, blocks AMPH facilitation
and retards spontaneous recovery[3]

Reserpine
Catecholamine antagonist[3]
5 mg/kg, blocks AMPH facilitation
and retards spontaneous recovery

Alpha Receptor Agonists

Phenylephrine
NE alpha$_1$ receptor agonist
2, 4, or 8 mg/kg, N.S.
effects[4]

Prazosin
NE alpha$_1$ receptor
antagonist
2 or 4 mg/kg, N.S. effects

Clonidine
NE alpha$_2$ receptor agonist
.1 or .4 mg/kg, N.S. effects

Yohimbine
NE alpha$_2$ receptor
antagonist
.5 or 5 mg/kg, N.S. effects
10 mg/kg, significant
facilitation

Idazoxan
NE alpha$_2$ receptor
antagonist
1.0 mg/kg, N.S. effects
2.0 mg/kg, significant
facilitation[2]

Apomorphine
Dopamine receptor agonist
0.2 to 20 mg/kg, N.S. effects

Footnotes

1. Causes release, blocks the reuptake, and acts as false transmitter at

NE, DA, 5-HT synapses. Effects other neurotransmitter systems as well.

2. Higher doses evoke stereotopies that interfere with the observation of facilitory effects on recovery of beam walking following TBI.

3. Replicated in cat.

4. N.S. effect replicated without prodding during BW testing, see ref. 7.

5. Effects both noradrenergic and dopaminergic systems.

6. Only when massed trials are given during drug intoxication.

APPENDIX 1-B

SENSORIMOTOR CORTEX CONTUSION (TBI) MODEL

DRUGS TESTED FOR EFFECTS ON RECOVERY RATE

Catecholamine Agonists

Amphetamine
Monoamine agonist[1]
2 mg/kg, significant facilitation

Catecholamine Antagonists

Haloperidol
Catecholamine antagonist[3]
.4 mg/kg, blocks AMPH facilitation and retards recovery

Non-catecholamine Agonists

Morphine
Opiate receptor agonist[2]
5 or 20 mg/kg, N.S. effects
10 mg/kg, significant facilitation

Specific Receptor Agonists

Methoxamine
NE alpha$_1$ receptor agonist
1, 4, or 8 mg/kg, N.S. effects

Prazosin
NE alpha$_1$ receptor antagonist
4 mg/kg, significant retardation

Yohimbine
NE alpha$_2$ receptor antagonist
10 mg/kg, N.S. effects

Propranolol
NE beta$_{1\ \&\ 2}$ receptor antagonist
10 mg/kg, N.S. effects

Footnotes

1. Causes release, blocks the reuptake, and acts as false transmitter at NE, DA, 5-HT synapses. Effects other neurotransmitter systems as well.

2. May have effect through noradrenergic mechanism since morphine can release NE from LC terminals.

3. Effects both noradrenergic and dopaminergic systems.

APPENDIX 1-C

DRUGS TESTED FOR REINSTATEMENT OF HEMIPLEGIC SYMPTOMS IN ANIMALS RECOVERED FROM SMCX INJURY

Ablation model

Prazosin
NE $alpha_1$ receptor antagonist
2 or 4 mg/kg, Significant reinstatement

Phenoxybenzamine
NE $alpha_1$ receptor antagonist
10 mg/kg, Significant reinstatement[2,3]

Clonidine
NE $alpha_2$ receptor agonist
.1 or .4 mg/kg, Significant reinstatement[2]

Yohimbine
NE $alpha_2$ receptor antagonist
.5, 5, or 10 mg/kg, N.S. effects

Propranolol
NE $beta_{1\ \&\ 2}$ receptor antagonist
20 mg/kg, N.S. effects

Pentobarbital
Effects many systems
5 mg/kg, for 5 days
N.S. effects[2]

Contusion model

Prazosin
NE $alpha_1$ receptor antagonist
4 mg/kg, Significant reinstatement

Phenoxybenzamine
NE $alpha_1$ receptor antagonist
10 mg/kg, Significant reinstatement[2,3]

Clonidine
NE $alpha_2$ receptor agonist
.4 mg/kg, significant reinstatement

Propranolol
NE $beta_{1\ \&\ 2}$ receptor antagonist
10 mg/kg, N.S. effects

Haloperidol
Catecholamine antagonist[1]
.4 mg/kg, Significant reinstatement effects only with chronic administration

Footnotes

1. Effects both noradrenergic and dopaminergic systems.

2. Replicated in cat ablation

3. Blocks AMPH/SRE facilitation of recovery in embolic stroke model.

APPENEDIX 2

ARTICLES CITING THE ARMY CONTRACT [DAMD17-86-C-6144]

Sutton R.L. and Feeney, D.M. (1991) Effects of Alpha-Noradrenergic Agonists and Antagonists on Recovery and Maintenance of Beam-walking Ability after Sensorimotor Cortex Abaltion in the Rat. Restorative Neurology and Neuroscience, In Press.

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